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(71) Applicant: Mitsubishi Yuka Pharmaceutical Co., Ltd.
3-7, Ginza 8-chome Chuo-ku
Tokyo104(JP)

(72) Inventor: Sekiya, Tetsuo Research Lab. Mitsubishi Yuka Pharmaceut. Co. Ltd. 500 Aza Furuki Oaza Wakaguri Amimachi Inashiki-gun Ibaraki-ken(JP)

(72) Inventor: Tsutsui, Mikio Research Lab. Mitsubishi Yuka Pharmaceut. Co. Ltd. 500 Aza Furuki Oaza Wakaguri Amimachi Inashiki-gun Ibaraki-ken(JP)

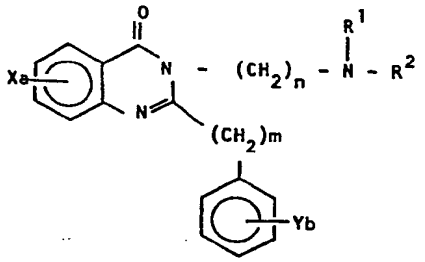
(72) Inventor: Horii, Daijiro Research Lab. Mitsubishi Yuka Pharmaceut. Co. Ltd. 500 Aza Furuki Oaza Wakaguri Amimachi Inashiki-gun Ibaraki-ken(JP)

(72) Inventor: Ishibashi, Akira Research Lab. Mitsubishi Yuka Pharmaceut. Co. Ltd. 500 Aza Furuki Oaza Wakaguri Amimachi Inashiki-gun Ibaraki-ken(JP)

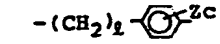
(74) Representative: Eitle, Werner, Dipl.-Ing. et al,
Hoffmann, Eitle & Partner Patentanwälte Arabellastrasse 4
D-8000 München 81(DE)

(54) **2-Phenylalkyl-3-aminoalkyl-4(3H)-quinazolinones, processes for preparing them, pharmaceutical compositions and use.**

(57) Disclosed are a 2-phenylalkyl-3-aminoalkyl-4(3H)-quinazolinone compound of Formula (1):



werein, X represents a hydrogen at m, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a phenoxy group, a benzyl xy group, a halogen atom or a hydroxy gr up; Y represents an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a benzyloxy group, a halogen atom or a nitro group; R^1 represents a hydrogen atom or an alkyl group having 1 to 5 carbon atoms; R^2 represents an alkyl group having 1 to 5 carbon atoms or a group of Formula (2)



[wherein, Z represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, or a halogen atom; is an integer of 1 to 3; and ℓ is an integer of 1 to 5]; or R^1 and R^2 represent together with the nitrogen atom to which they are attached, a cyclic amin group of the formula:

./...

[wherein, A represents an alkylene group having 2 to 6 carbon atoms or a group of the formula $-(CH_2)_2-O-(CH_2)_2-$]; a and b are independently an integer of 1 to 3; and n and m are independently an integer of 1 to 5, or a pharmaceutically acceptable acid addition salt thereof, a process for preparing said compound, a composition comprising said compound as an active ingredient and a use of the said compound for the preparing of a pharmaceutical composition.

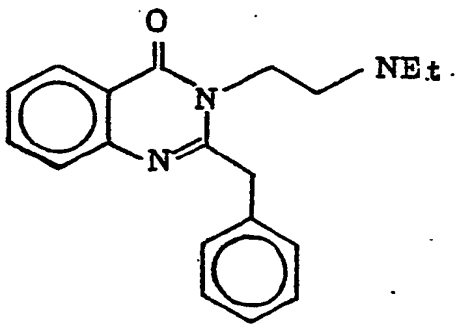
The compounds of the present invention have calcium antagonistic, vasodilative, and antihypertensive activities.

2-Phenylalkyl-3-aminoalkyl-4(3H)-quinazolinones, Processes for Preparing Them, Pharmaceutical Compositions and Use

BACKGROUND OF THE INVENTION

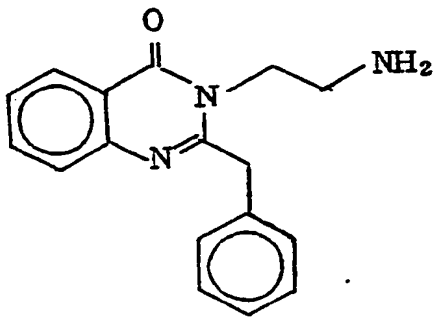
This invention ralates to a novel 4(3H)-quinazolinone compound, and more particularly, a 2-phenylalkyl-3-aminoalkyl-4(3H)-quinazolinone compound having calcium antagonistic, vasodilative, and antihypertensive activities, or a parmaceutically acceptable acid addition salt thereof, to a process for preparing said compound, to a composition having calcium antagonistic activity and comprising said compound as an active ingredient, and to the use for preparing a composition for the dilating of blood vessels or reducing the level of blood pressure based on calcium antagonistic activity.

With respect to a 2-phenylalkyl-3-aminoalkyl-4(3H)-quinazolinone derivative, there has been reported that 2-phenylmethyl-3-(2-diethylaminoethyl)-4(3H)-quinazolinone of the formula:



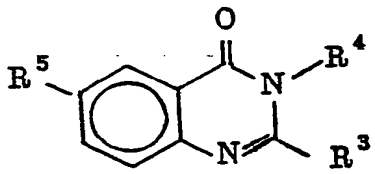
has an antispasmodic activity [Arzneim. Forch. 13, 688 (1963)].

Moreover, although there has been known 2-phenylmethyl-3-(2-aminoethyl)-4(3H)-quinazolinone of the formula:



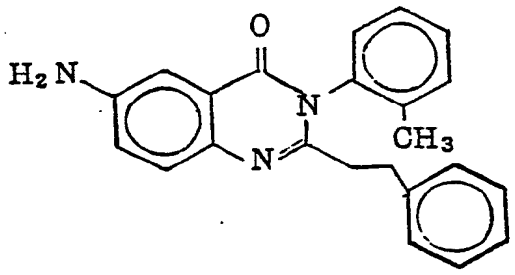
any pharmacological activity thereof has not been reported [J. Indian Chem. Soc.,57, 835 (1980)].

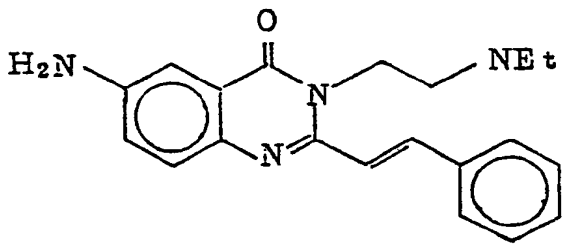
Further, in U. S. Patent No.3,558,610, there has been described that a 4(3H)-quinazolinone derivative of the general formula:



wherein, R^3 represents a phenyl alkyl group, etc.; R^4 represents a di-lower alkylamino group, etc.; R^5 represents an amino group, an alkanoylamino group, a benzylideneamino group or a nitrofurylideneamino group,

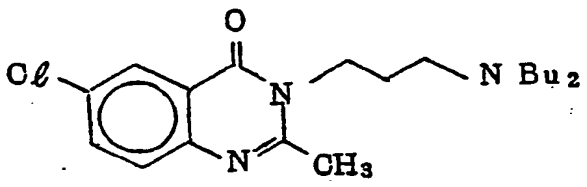
is useful as an anti-inflammatory or antimicrobial agent. However, of the compounds described in the Examples of the above Patent, compounds in which R^3 is a phenylalkyl group, or R^4 is a di-lower alkylamino group are only two compounds of the following formulas:





and there have been described no compounds in which R_3 is a phenylalkyl group and simultaneously R^4 is a di-lower alkylamino group. The compounds disclosed therein are ones in which R^5 is always an amino group or a substituted amino group and are different from the compounds of the present invention.

Still further, there has been reported that 2-methyl-3-(3-dibutylaminopropyl)-6-chloro-4(3H)-quinazolinone of the following formula:

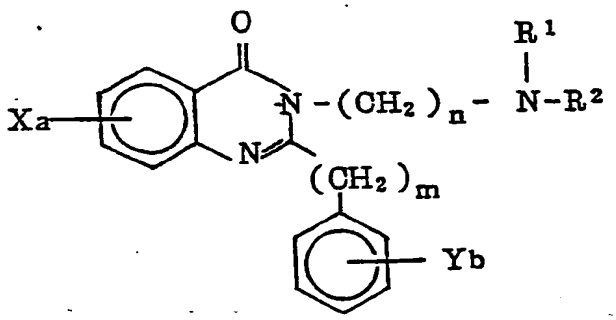


has the inhibitive activity of acetylcolinesterase, although it is not a 2-phenylalkyl-3-aminoalkyl- 4(3H)-quinazolinone derivative [Indian J. Pharm., 33, 80 (1971)].

THE SUMMARY OF THE INVENTION

An object of the present invention is to provide a novel and useful 2-phenylalkyl-3-aminoalkyl-4(3H)-quinazolinone derivative.

Based on the knowledge described above, the present inventors have made intensive studies, and as a result, have accomplished the present invention. Namely, the novel and useful 2-phenylalkyl-3-aminoalkyl-4(3H)-quinazolinone derivative of the present invention is a compound of Formula (1):



— (1)

wherein, X represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a phenoxy group, a benzyloxy group, a halogen atom or a hydroxy group; Y represents an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a benzyloxy group, a halogen atom or a nitro group; R^1 represents a hydrogen atom or an alkyl group having 1 to 5 carbon atoms; R^2 represents an alkyl group having 1 to 5 carbon atoms or a group of Formula (2) $-(CH_2)_{\ell}-C_6H_4-Z_c$ [wherein, Z represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms or a halogen atom; c is an integer of 1 to 3; and ℓ is an integer of 1 to 5]; or R^1 and R^2 represent together with the nitrogen atom to which they are attached, a cyclic amino group of the formula: $-N\frown A$ [wherein, A represents an alkylene group having 2 to 6 carbon atoms or a group of the formula $-(CH_2)_2-O-(CH_2)_2-$]; a and b are independently an integer of 1 to 3; and n and m are independently an integer of 1 to 5,

or a pharmaceutically acceptable acid addition salt thereof.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In above Formula (1), the alkyl group having 1 to 5 carbon atoms represented by X or Y includes, for example, a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, a sec-butyl group, and a pentyl group; the alkoxy group having 1 to 5 carbon atoms represented by X or Y includes, for example, a

methoxy group, an ethoxy group, an n-propoxy group, an isopropoxy group, an n-butoxy group, a sec-butoxy group, an n-pentoxy group and an isopentoxy group; and the halogen atom represented by X or Y includes a fluorine atom, a chlorine atom, a bromine atom and an iodine atom.

The alkyl group having 1 to 5 carbon atoms of R^1 or R^2 includes, for example, a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, a sec-butyl group and a pentyl group. In cases where R_2 is an aralkyl group represented by Formula (2), the alkyl group having 1 to 5 carbon atoms represented by Z includes, for example, a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, a sec-butyl group and a pentyl group; the alkoxy group having 1 to 5 carbon atoms represented by Z includes, for example, a methoxy group, an ethoxy group, an n-propoxy group, an isopropoxy group, an n-butoxy group, a sec-butoxy group and an n-pentoxy group; and the halogen atom represented by Z includes a fluorine atom, a chlorine atom, a bromine atom and an iodine atom. The cyclic amino group of the formula: $-N\overset{\frown}{\underset{\smile}{}}A$, which is formed by R^1 and R^2 together with the nitrogen atom to which they are attached, includes, for example, an azilidino group, a pyrrolidino group, a pyperidino group, a hexamethyleneimino group and a morpholino group. X, Y and Z each may be mono-substituted, di-substituted or tri-substituted. In cases where X is di-substituted or tri-substituted, the substituents thereof may be the same or different. In cases where Y is di-substituted or tri-substituted, the substituents thereof may be the same or different. In cases where Z is di-substituted or tri-substituted, the substituents thereof may be the same or different.

The term "pharmaceutically acceptable acid addition salt" used herein means an addition salt of an acid which does

not increase substantially toxicity of the basic compound.

These acid addition salts include, for example, a salt with an mineral acid such as hydrochloric acid, sulfuric acid and phosphoric acid, and with an organic acid such as acetic acid, malonic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, methanesulfonic acid, paratoluenesulfonic acid and glucuronic acid. Such an acid addition salt can be obtained by dissolving the compound of the present invention in a suitable solvent and then adding thereto an acid as such or after dissolved in a suitable solvent. The suitable solvent includes, for example, ether and ethanol.

The compounds of the present invention have a pharmacological activity such as calcium antagonistic activity, vasodilative activity, antihypertensive activity and the like, and are useful as medical preparations for a cardiopathy and a circulatory disease. Moreover, these compounds are also useful as active ingredients for pharmaceutical preparations having activities of dilating blood vessels and enhancing effects of carcinostatics based on the calcium antagonistic activity.

The compound of the present invention may be administered orally or parenterally to a human being in an ordinary manner. When orally administered, it is preferable to administer the compound in an amount of 1 to 100 mg per one dosage, 1 to 3 times a day; when administered by intravenous injection, it is preferable to administer the compound in an amount of 0.01 to 10 mg 1 per one dosage, 1 to 5 times a day; and when administered through intestinum rectum, it is preferable to administer the compound in an amount of 1 to 100 mg per one dosage, 1 to

3 times a day. Compound (1) of the present invention or a salt thereof is generally administered in a form of a composition containing a carrier, a vehicle and the other additives usualluy employed for medical preparations. The medical carrier may be either solid or liquid and the solid carrier includes, for example, lactose, kaoline, starch, crystalline cellulose, corn starch, talc, agar, pectin, acacia, stearic acid, magnesium stearate, lecthin, sodium chloride and the like. The liquid carrier includes, for example, syrup, glycerin, peanut oil, polyvinylpyrrolidone, olive oil, ethanol, benzyl alcohol, propylene glycol, water and the like.

The medical preparations containing the compound of the present invention may take various forms. When the solid carrier is used, they may take a form of tablets; powders; granules; powders or granules encapsulated in a hard gelatin; suppositories or troches.

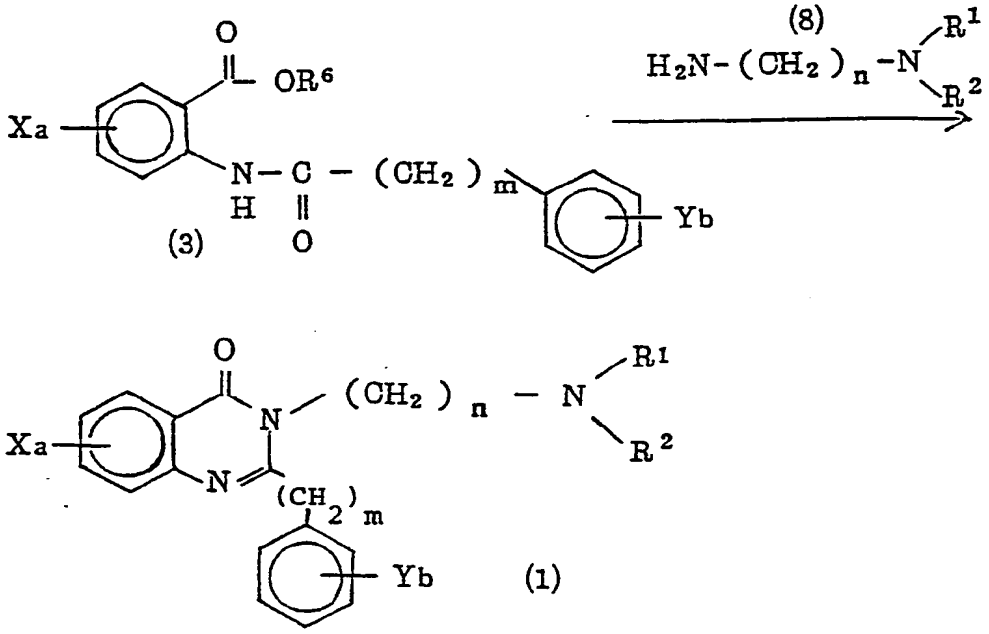
When the liquid carrier is used, the medical preparations may take a form of syrups; emulsions; soft gelatin capsules; sterilized injections, for example, sealed in an ampul, or aqueous or non-aqueous suspensions.

The compound of Formula (1) of the present invention may be also used as a cyclodextrin clathrate compound or through procedures of incorporating the compound of the present invention or the salt thereof in a ribosome.

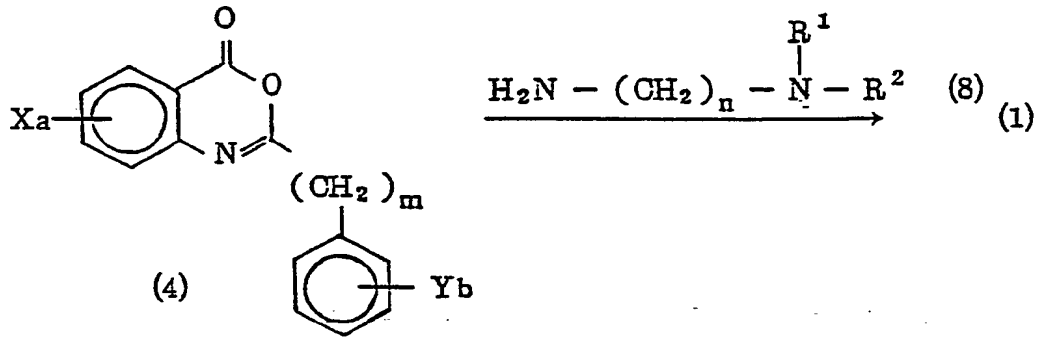
Methods for preparing the compound of the present invention will be described below.

The compound of Formula (1) of the present invention can be prepared, for example, according to the following Synthesis process s A to E.

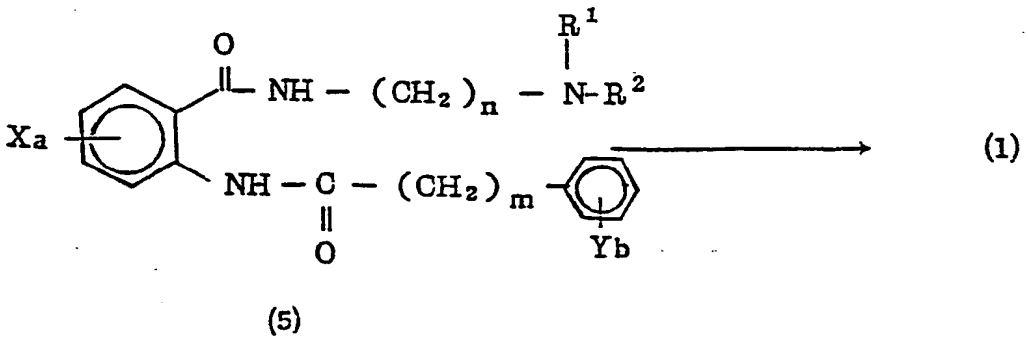
Synthesis process A



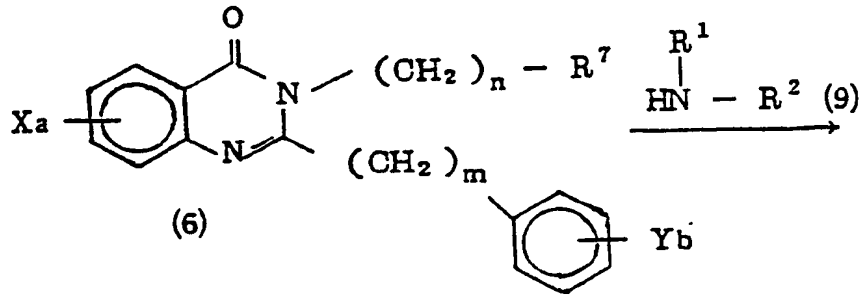
Synthesis process B



Synthesis process C

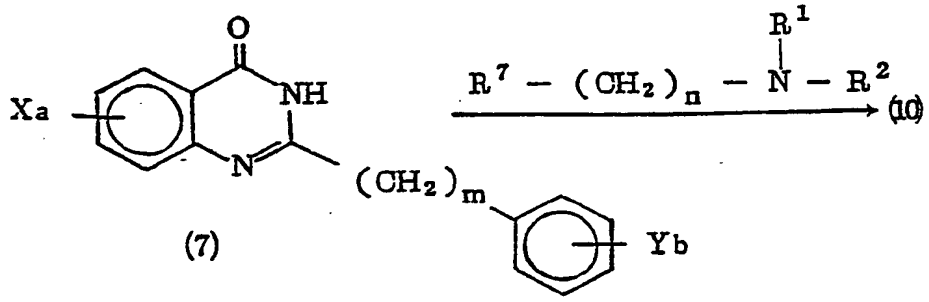


Synthesis process D



(1)

Synthesis process E



(1)

wherein, X, Y, R^1, R^2, a, b, m and n have the same meanings as defined above; R^6 represents a hydrogen atom and an alkyl group having 1 to 5 carbon atoms; and R^7 represents a halogen atom or a mesyloxy or tosyloxy group.

Synthesis process A

Synthesis process A is a method for preparing the compound of Formula (1) in which an N-(phenylalkylcarbonyl) anthranilic acid or an ester thereof (3) and a diamine (8) are condensed to form a ring therebetween. The diamine (8) may be used in an amount of 0.5 to 5 equivalent to the anthranilic acid or the ester thereof (3). The reaction solvent, although not restricted if it does not participate in the reaction, includes, for example, aromatic hydrocarbons

such as benzene, toluene and xylene; ethers such as tetrahydrofuran, dioxane and ethylene glycol diethyl ether; ketones such as acetone and methyl ethyl ketone; ethyl acetate; dimethylformamide; dimethylacetamide; dimethyl sulfoxide and the like. The reaction temperature may be in the range of from 0 to 250°C and preferably from 100 to 200°C. The reaction time may be in the range of from 30 minutes to 48 hours and preferably 1 to 24 hours. If desired , an acid or a base may be added to the reaction system as a catalyst.

Synthesis process B

Synthesis process B is a method for preparing the compound of Formula (1) in which a 2-phenylalkyl-4H-3,1-benzoxazine-4-one (4) and a diamine (8) are condensed to form a ring therebetween. The diamine (8) may be used in an amount of 0.5 to 5 equivalent to the 4H-3,1-benzoxazin-4-one (4). The reaction solvent, although not restricted if it does not participate in the reaction, includes, for example, aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as tetrahydrofuran, dioxane and ethylene glycol diethyl ether; ketones such as acetone and methyl ethyl ketone; ethyl acetate; dimethylformamide; dimethylacetamide; dimethyl sulfoxide and the like. The reaction temperature may be in the range of from 0 to 250 °C and preferably from 50 to 150 °C. The reaction time may be in the range of from 30 minutes to 48 hours and preferably 1 to 24 hours. If desired, an acid or a base may be added to the reaction system as a catalyst.

Synthesis process C

Synthesis process C is a method for preparing the compound of Formula (1) in which an N-substituted

aminoalkyl-2-phenylalkylcarbonylaminobenzoic amide (5) is condensed to form a ring. The reaction may be carried out without any solvent or in an solvent which does not participate in the reaction, for example, aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as tetrahydrofuran, dioxane and ethylene glycol diethyl ether; ketones such as acetone and methyl ethyl ketone; ethyl acetate; acetic anhydride; dimethylformamide; dimethylacetamide; dimethyl sulfoxide and the like. The reaction temperature may be in the range of from 0 to 250 °C and preferably from 100 to 150 °C. The reaction time may be in the range of from 30 minutes to 48 hours and preferably 1 to 24 hours. If the case demands, an acid may be added to the reaction system as a catalyst.

Synthesis process D

Synthesis process D is a method for preparing the compound of Formula (1) in which a 2-phenylalkyl-3-(halogenoalkyl or sulfonyloxyalkyl)-4(3H)-quinazolinone derivative (6) and an amine (9) are subjected to raction with each other. The amine (9) may be used in an amount of 0.5 to 5 equivalent to the 4(3H)-quinanzolinone derivative (6). The reaction solvent, although not restricted if it is inert to the reaction, includes, for example, aromatic hydrocarbons such as benzene, toluene and xylene; alcohols such as methanol, ethanol and isoamyl alcohol; ethers such as tetrahydrofuran, dioxane and ethylene glycol diethyl ether; ketones such as acetone and methyl ethyl ketone; ethyl acetate; dimethylformamide; dimethylacetamide; dimethyl sulfoxide and the like. The reaction temperature may be in the range of from 0 to 250 °C and preferably from 50 to 150 °C. The reaction time may be in the range of from 30 minutes to 48 hours and preferably 1 to 24 hours. When the reaction is carried out, an excess of the amine (9),

for example, an organic amine such as triethylamine, pyridine, diazacycloundecene (DBU), or an inorganic base such as sodium hydroxide, potassium hydroxide, sodium carbonate, sodium hydrogencarbonate should preferably be present in the reaction system as an acid removing agent, for the smooth progress of the reaction.

Synthesis process E

Synthesis process E is a method for preparing the compound of Formula (1) in which a 2-phenylmethyl-4(3H)-quinazolinone (7) and an aminoalkyl halide (or an aminoalkyl sulfonate) (10) are subjected to raction with each other. The aminoalkyl halide (or the aminoalkyl sulfonate) (10) may be used in an amount of 0.5 to 5 equivalent to the 4(3H)-quinazolinone (7). The reaction solvent, although not restricted if it is inert to the reaction, includes, for example, aromatic hydrocarbons such as benzene, toluene and xylene; alcohols such as methanol, ethanol and isoamyl alcohol; ethers such as tetrahydrofuran, dioxane and ethylene glycol diethyl ether; ketones such as acetone and methyl ethyl ketone; ethyl acetate; dimethyl-formamide; dimethylacetamide; dimethyl sulfoxide and the like. The reaction temperature may be in the range of from 0 to 250 ^{o}C and preferably from 50 to 150 ^{o}C. The reaction time may be in the range of from 30 minutes to 48 hours and preferably 1 to 24 hours. When the reaction is carried out in the presence of a base such as sodium metal, sodium hydride, potassium t-butoxide, the reaction proceeds smoothly.

Next, the present invention will be explained more specifically by the following Examples, by which however the present invention should not be limited.

Example

Synthesis example 1

N-(2-Methoxyphenylacetyl)-anthranilic acid methyl ester:

To a mixed solution of acetone (300 ml) and a 6 % aqueous potassium carbonate solution (200 ml) there were added 10.2 g (67 mmol) of methyl ester of anthranilic acid. 12.5 g (67 mmol) of 2-Methoxyphenylacetic acid chloride were added dropwise under cooling thereto and the resulting reaction mixture was stirred at room temperature for 4 hours. The resulting precipitates were collected by filtration to obtain 15.7 g (yield 78 %) of N-(2-methoxyphenylacetyl)-anthranilic acid methyl ester.

m.p. : 116 - 117 °C.

Example 1

2-(2-Methoxyphenylmethyl)-3-(2-diethylaminoethyl)-4(3H)-quinazolinone hydrochloride (Compound No.1; Synthesis process A)

A solution of 3.0 g (10 mmol) of methyl ester of N-(2-methoxyphenyl-acetyl)-anthranilic acid and 5.1 g (50 mmol) of 2-diethylaminoethylamine in ethanol (20 ml) was heated at 180°C for 7 hours in a seald tube. After cooling, the thus obtained reaction mixture was purified by silica gel column chromatography (eluent; chloroform : ethanol = 98 : 2) to obtain 1.24 g (yield 34 %) of 2-(2-methoxyphenylmethyl)-3-(2-diethylaminoethyl)-4(3H)-quinazolinone as an oily substance. 1.2 g of the oily substance were dissolved in ethanol (5 ml) and a 7 % HCl-ethanol solution (1.5 ml) were added thereto. The resulting solution was allowed to cool overnight. The

r sulting colorless precipitates were collected by filtration to obtain 1.0 g of the captioned hydrochloride which is the desired compound.

m.p.: 196 - 209 °C (decomposition)

Infrared absorption spectrum (IR) (cm^{-1}):
1670 (C=O),
1590 (phenyl group)

Analysis Calculated for $C_{22}H_{27}N_3O_2$ HCl:

C, 65.74; H, 6.77; N, 10.46 %

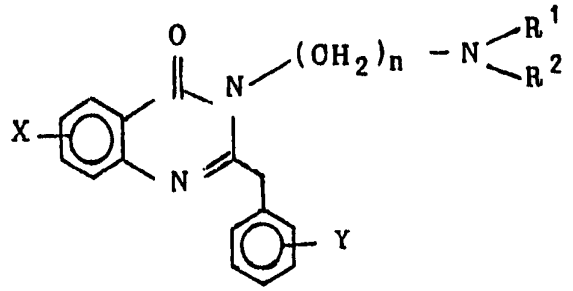
Found: C, 65.57; H, 7.01; N, 10.44 %

Examples 2 to 29

2-(Substituted phenylmethyl)-3-(substituted aminoalkyl)-4 (3H)-quinazolinone derivatives (Compound Nos. 2 to 29)

The captioned compounds were synthsized in the same manner as in Example 1 except that the methyl ester of N-(2-methoxyphenylacetyl)anthranilic acid was replaced by corresponding esters of anthranilic acid, and the 2-diethylaminoethylamine was replaced by the corresponding diamines. The results obtained are shown in Table 1.

Table 1



Example No.	Compound No.	X	Y	$N\begin{matrix}R^1\\R^2\end{matrix}$	n	Discrimination between free base and salt	Ester form of starting material	Yield (%)	Melting point (°C)	Infrared absorption spectrum (cm^{-1})
2	2	hydrogen atom	2-chloro	diethylamino	2	hydrochloride	ethyl	57	188-193	1665 1590
3	3	"	4-chloro	"	2	"	methyl	10	175-178	1670 1585
4	4	"	2-chloro	"	2	"	ethyl	36	191-194	1670 1590
5	5	"	3-chloro	"	2	"	methyl	36	210-213	1675 1590
6	6	"	4-chloro	"	2	fumarate	ethyl	14	160-165	1675 1590
7	7	"	4-bromo	"	2	free base	methyl	27	(oily)	1670 1590
8	8	"	4-methoxy	"	2	"	ethyl	61	(oily)	1670 1590
9	9	"	2-ethoxy	"	2	hydrochloride	methyl	17	159-162	1665 1585
10	10	"	4-ethoxy	"	2	"	"	42	173-184	1670 1585
11	11	"	4-methyl	"	2	"	ethyl	62	162-168	1660 1590
12	12	"	4-nitro	"	2	free base	"	9	114-122	1665 1585
13	13	"	2,5-dimethoxy	"	2	hydrochloride	"	42	179-181	1670 1590

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Table 1 (Contd.)

Example No.	Compound No.	X	Y	$N\begin{smallmatrix}R^1\\R^2\end{smallmatrix}$	n	Discrimination between free base and salt	Ester form of starting material	Yield (%)	Melting point (°C)	Infrared absorption spectrum (cm^{-1})
14	14	hydrogen atom	2,5-dimethoxy	diethylamino	3	hydrochloride	methyl	8	120-124	1675 1590
15	15	"	"	pyrrolidino	2	"	"	25	124-128	1670 1585
16	16	"	"	dimethylamino	2	"	"	23	189-194	1660 1580
17	17	"	"	"	3	"	"	14	212-216	1665 1595
18	18	"	3,4-dimethoxy	diethylamino	2	free base	ethyl	77	(oily)	1660 1585
19	19	"	2-benzyloxy	"	2	hydrochloride	methyl	30	182-189	1665 1585
20	20	"	4-benzyloxy	"	2	"	"	45	137-138	1670 1590
21	21	6-methyl	2,5-dimethoxy	"	2	"	"	13	152-155	1660 1580
22	22	"	"	"	3	free base	"	20	(oily)	1660 1580
23	23	"	"	morpholino	3	"	"	24	(")	1665 1585
24	24	"	"	dimethylamino	2	hydrochloride	"	13	187-198	1655 1575
25	25	6-iodo	2-methoxy	diethylamino	2	"	"	54	189-194	1670 1585
26	26	"	2,5-dimethoxy	"	2	"	"	49	164-168	1670 1585
27	27	"	4-ethoxy	"	2	"	"	60	193-195	1670 1580
28	28	6-chloro	2,5-dimethoxy	"	2	"	"	44	162-163	1670 1585
29	29	7-chloro	"	"	2	"	"	46	146-150	1680 1590

Synthesis example 2

2-(2,5-Dimethoxyphenylmethyl)-6-isopropoxy-4H-3,1,-benzoxazin-4-one

To a suspension of 9.8 g (50 mmol) of 5-isopropoxy-2-aminobenzoic acid and 11.0 g (80 mmol) of potassium carbonate in a mixed solvent of acetone (40 ml) and water (40 ml), 10.5 g (50 mmol) of 2,5-dimethoxyphenylacetic acid chloride were added dropwise at 10 °C. After the resulting reaction mixture was stirred under ice cooling for 1 hour, stirring was continued for further 2 hours at room temperature. The thus obtained solution was made acidic with conc. hydrochloric acid and extracted with dichloromethane. After the extract was dried over magnesium sulfate, the solvent was distilled off to obtain 14.0 g (75%) of 2-(2,5-dimethoxyphenyl-acetylamino)-5-isopropoxybenzoic acid (m.p. 132 - 135 °C). Then the thus obtained acid was heated under reflux for 2 hours in acetic anhydride (100 ml), followed by concentration under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent: dichloromethane) to obtain 6.8 g of 2-(2,5-dimethoxyphenylmethyl)-6-isopropoxy-4H-3,1-benzoxazine-4-one (yield from 5-isopropoxy-2-aminobenzoic acid: 36 %)

m.p. 84 - 87 °C

Infrared absorption spectrum (cm^{-1}): 1745, 1630

Example 30

2-(2,5-Dimethoxyphenylmethyl)-3-(3-dimetylaminopropyl)-6-isopropoxy-4(3H)-quinazolinone maleate (Compound No. 30; Synthesis process B)

2.84 g (8 mmol) of 2-(2,5-dimethoxyphenylmethyl)-6-isopropoxy-4H-3,1-benzoxazin-4-one and 0.82 g (8 mmol) of 3-dimethylaminopropylamine were heated under reflux for 15 hours in xylene (20 ml). After the xylene was distilled off, the residue obtained was purified by silica gel column chromatography (eluent; 2 % ethanol/chloroform) to obtain 1.46 g (42 %) of 2-(2,5-dimethoxyphenylmethyl)-3-(3-dimethylaminopropyl)-6-isopropoxy-4(3H)-quinazolinone as an oily substance. Subsequently, 0.22 g of the 2-(2,5-dimethoxyphenylmethyl)-3-(3-dimethylamino-propyl)-6-isopropoxy-4(3H)-quinazolinone was dissolved in ether (15 ml) and to the resulting soluion, there was added an ethanolic solution containing 0.07 g (0.6 mmol) of maleic acid. The thus obtained solution was allowed to stand for one day. The precipitated colorless crystals were collected by filtration to obtain 0.25 g of the maleate which is the desired compound.

m.p.: 188 - 189 °C

Mass spectrum (m/e): 439 (M^+),
58 (Base peak ion)

Analysis Calculated for $C_{25}H_{33}N_3O_4 \cdot C_4H_4O_4$:

C, 62.68; H, 6.71; N, 7.56 %

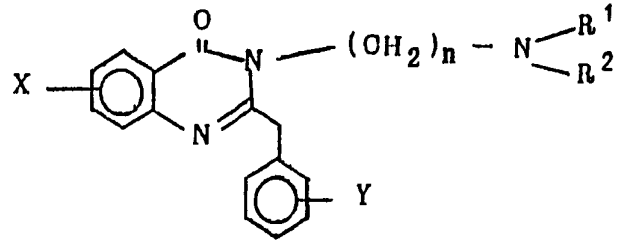
Found: C, 62.48; H, 6.71; N, 7.57 %

Examples 31 to 88

2-(Substituted phenylmethyl)-3-(substituted aminoalkyl)-4(3H)-quinazolinone derivatives, (Compound Nos.31 to 88)

The captioned compounds were synthsized in the same manner as in Example 30 except that the 2-(2,5-dimethoxyphenylmethyl)-6-isopropoxy-4H-3,1-benzoxazin-4-one was replaced by the corresponding 4H-3,1-benzoxazin-4-one, and the 3-dimethylaminopropylamine was replaced by the corresponding diamines. The results obtained are shown in Table 2.

Table 2



Example No.	Compound No.	X	Y	$N\begin{matrix}R^1\\R^2\end{matrix}$	n	Discrimination between free base and salt	Yield (%)	Melting point (°C)	Mass spectrum (m/e) M^+	Mass spectrum (m/e) Base peak ion
31	31	6-methyl	2,5-dimethoxy	pyrrolidino	2	fumarate	75	169-170	407	84
32	32	"	"	"	3	free base	54	oily	421	84
33	33	6-ethyl	"	dimethylamino	3	"	50	"	409	58
34	34	"	"	diethylamino	3	"	48	"	437	86
35	35	7-chloro	"	dimethylamino	3	hydrochloride	90	186-192	415	58
36	36	"	"	pyrrolidino	3	free base	45	oily	441	84
37	37	"	"	diethylamino	3	"	68	"	443	86
38	38	6-hydroxy	"	pyrrolidino	2	"	38	"	409	84
39	39	"	"	dimethylamino	3	"	38	"	397	58
40	40	6-methoxy	"	"	3	"	5	"	411	58
41	41	6-ethoxy	2-methoxy	"	2	hydrochloride	83	209-216	381	58

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Table 2 (Contd.)

Example No.	Compound No.	X	Y	$N(R^1)(R^2)$	n	Discrimination between free base and salt	Yield (%)	Melting point (°C)	Mass spectrum (m/e) M^+	Mass spectrum (m/e) Base peak ion
42	42	6-ethoxy	4-methoxy	dimethylamino	2	hydrochloride	83	235-240	381	58
43	43	"	2,5-dimethoxy	"	2	"	83	214-217	411	58
44	44	6-n-propoxy	"	pyrrolidino	2	"	69	132-137	416	84
45	45	"	"	diethylamino	2	"	82	154-159	453	86
46	46	6-isopropoxy	"	pyrrolidino	2	"	32	141-147	451	84
47	47	"	"	dimethylamino	2	"	61	184-188	425	58
48	48	"	"	diethylamino	2	"	76	154-158	453	86
49	49	"	"	pyrrolidino	3	"	48	125-130	465	84
50	50	"	4-methoxy	dimethylamino	2	"	46	195-199	395	58
51	51	"	2-chloro	"	2	free base	50	oily	399	58
52	52	"	4-chloro	"	2	"	51	"	389	58
53	53	"	4-methoxy	"	3	"	35	"	409	58
54	54	6-n-butoxy	2,5-dimethoxy	"	3	hydrochloride	51	184-188	453	58
55	55	"	"	pyrrolidino	2	"	89	166-173	465	84
56	56	"	"	diethylamino	2	"	53	150-157	468	86
57	57	"	"	dimethylamino	2	"	83	130-138	439	58
58	58	6-isobutoxy	"	pyrrolidino	2	"	33	154-161	465	84
59	59	"	"	dimethylamino	3	free base	31	oily	453	58

Table 2 (Contd.)

Example No.	Compound No.	X	Y	$N\begin{smallmatrix}R^1\\R^2\end{smallmatrix}$	n	Discrimination between free base and salt	Yield (%)	Melting point (°C)	Mass spectrum (m/e) M^+	Mass spectrum (m/e) Base peak ion
60	60	6-sec-butoxy	2,5-dimethoxy	dimethylamino	3	free base	31	oily	453	58
61	61	"	"	pyrrolidino	2	hydrochloride	57	147-153	465	84
62	62	"	"	diethylamino	2	free base	19	oily	467	86
63	63	"	"	dimethylamino	2	hydrochloride	92	116-125	439	58
64	64	"	"	"	3	"	71	185-190	453	58
65	65	6-n-pentoxy	"	"	3	"	72	210-214	467	58
66	66	"	"	pyrrolidino	2	"	68	127-135	479	84
67	67	"	"	"	3	free base	60	oily	493	84
68	68	"	"	dimethylamino	3	"	63	"	495	86
69	69	"	"	"	2	hydrochloride	59	123-129	481	86
70	70	"	"	"	2	"	70	141-150	453	58
71	71	6-isopentoxy	"	pyrrolidino	2	"	82	140-148	479	84
72	72	"	"	"	3	"	59	99-103	493	84
73	73	"	"	dimethylamino	3	free base	56	oily	467	58
74	74	"	"	"	2	hydrochloride	65	129-137	453	58
75	75	"	"	diethylamino	2	"	63	131-138	481	86
76	76	"	"	"	3	free base	43	oily	495	86

Table 2 (Contd.)

Example No.	Compound No.	X	Y	$N\begin{smallmatrix}R^1\\R^2\end{smallmatrix}$	n	Discrimination between free base and salt	Yield (%)	Melting point (°C)	Mass spectrum (m/e) M^+	Mass spectrum (m/e) Base peak ion
77	77	6,7-dimethoxy	2,5-dimethoxy	dimethylamino	2	free base	64	oily	427	58
78	78	"	4-methoxy	"	2	"	73	"	397	58
79	79	6-methoxy-7-isopropoxy	2,5-dimethoxy	"	2	"	62	"	455	58
80	80	"	4-methoxy	"	2	"	45	"	425	58
81	81	6-isopropoxy-7-methoxy	2,5-dimethoxy	"	2	"	77	115-118	455	58
82	82	"	4-methoxy	"	2	hydrochloride	58	235-239	425	58
83	83	"	"	methylamino	2	free base	28	oily	411	355
84	84	6-ethoxy-7-methoxy	"	dimethylamino	2	"	77	"	411	58
85	85	"	"	"	3	"	77	"	425	58
86	86	6-isopropoxy	2-methoxy	"	2	hydrochloride	70	178-183	395	58
87	87	6-isopropoxy-7-methoxy	"	"	2	"	97	200-203	425	58
88	88	6-phenoxy	2,5-dimethoxy	"	2	"	49	184-187	459	58

Synthesis example 3

2-(2-Methoxyphenylmethyl)-4H-3,1-benzoxazin-4-one

Following the same procedure as in Synthesis example 2, 2-(2-methoxyphenylmethyl)-4H-3,1-benzoxazin-4-one was obtained from anthranilic acid and 2-(methoxyphenylacetic acid chloride as starting materials via 2-(2-methoxyphenylmethylcarbonyl amino)benzoic acid as an intermediate (yield: 60 %).

m.p. 102 - 104 °C

Mass spectrum (m/e): 267 (M^+), 146 (Base peak ion)

Infrared absorption spectrum (cm^{-1}): 1740, 1635, 1595

Example 89

2-(2-Methoxyphenylmethyl)-3-[2-{N-(3,4-dimethoxyphenylethyl)-N-methylamino}ethyl]-4(3H)-quinazolinone hydrochloride (Compound No. 89; Synthesis process B)

268 mg (1 mmol) of 2-(2-methoxyphenylmethyl)-4H-3,1-benzoxazine-4-one and 238 mg (1 mmol) of 2-[[N-[2-(3,4-dimethoxyphenyl)ethyl]-N-methylamino]]ethyl-amine were heated in xylene (10 ml) under reflux for 10 hours. After the xylene was distilled off, the residue obtained was purified by silica gel column chromatography (eluent; 2 % ethanol/chloroform) to obtain 107 mg (52 %) of 2-(2-methoxyphenylmethyl)-3-[2-{N-(3,4-dimethoxyphenylethyl)-N-methylamino}ethyl]-4(3H)-quinazolinone as an oily substance. Subsequently, the thus obtained quinazolinone was dissolved in ethanol (2 ml) and to the resulting soluion there was added a 7 % hydrogen chloride-ethanol solution (1 ml). Further, ether was

added to the reaction mixtur thus obtained, and the precipitated colorless crystals were collected by filtration to obtain 99 mg of the hydrochloride which is the desired compound.

m.p.: 171 - 175 °C (decomposition)

Mass spectrum (m/e): 487 (M^+),
293 (Base peak ion)

Analysis Calculated for $C_{29}H_{33}N_3O_4 \cdot HCl$:

C, 66.46; H, 6.54; N, 8.02 %

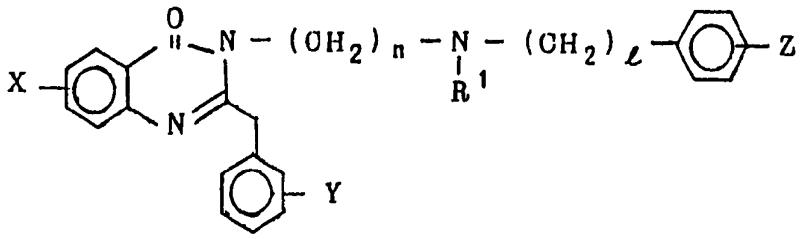
Found: C, 66.23; H, 6.75; N, 7.89 %

Examples 90 to 132

2-(Substituted phenylmethyl)-3-[N-alkyl-N-(substituted phenylalkyl)aminoalkyl]-4(3H)-quinazolinone derivatives (Compound Nos.90 to 132)

The captioned compounds were synthsized in the same manner as in Example 89 except that the 2-(2-methoxyphenylmethyl)-4H-3,1-benzoxazin-4-one was replaced by the corresponding 4H-3,1-benzoxazin-4-one derivatives, and the 2-[N-{2-(3,4-dimethoxyphenyl)ethyl}-N-methylamino]ethylamine was replaced by the corresponding N-alkyl-N-(substituted phenylalkyl)amino-alkylamines. The results obtained are shown in Table 3.

Table 3



No.	No.	X	Y	R^1	Z	n	ℓ	Discrimination between free base and salt	Yield (%)	Melting point (°C)	Mass spectrum (m/e) M^+	Mass spectrum (m/e) Base peak ion
90	90	hydrogen atom	2-methoxy	methyl	hydrogen atom	2	2	hydrochloride	51	180-210	427	293
91	91	"	"	"	"	2	1	"	50	175-185	413	134
92	92	"	"	"	"	3	2	free base	57	oily	441	307
93	93	"	2,5-dimethoxy	"	3,4-dimethoxy	2	2	"	23	"	-	337
94	94	"	4-chloro	"	hydrogen atom	2	2	hydrochloride	42	180-190	431	297
95	95	"	2-methyl	"	"	2	2	free base	53	oily	411	277
96	96	"	3-methyl	"	"	2	2	"	45	"	411	277
97	97	"	2-isoproxy	"	"	2	2	"	43	"	455	321
98	98	"	2-methoxy	"	"	2	3	"	75	"	441	293
99	99	"	"	"	"	2	4	hydrochloride	44	132-140	455	176
100	100	"	"	ethyl	"	2	2	free base	72	oily	441	162
101	101	"	"	buthyl	"	2	2	"	19	"	469	293

Table 3 (Contd.)

No.	No.	X	Y	R^1	Z	n	ℓ	Discrimination between free base and salt	Yield (%)	Melting point (°C)	Mass spectrum (m/e) M^+	Mass spectrum (m/e) Base peak ion
102	102	6-isopropoxy	2,5-dimethoxy	methyl	3,4-dimethoxy	2	2	free base	14	oily	575	381
103	103	"	"	"	"	3	2	"	11	"	589	395
104	104	"	"	"	hydrogen atom	3	2	"	9	"	529	395
105	105	6-sec-butoxy	"	"	3,4-dimethoxy	2	2	"	29	"	-	265
106	106	6-(4-chlorophenoxy)	"	"	"	2	2	hydrochloride	36	106-111	643	449
107	107	6-(4-methoxy-phenoxy)	"	"	"	2	2	"	23	100-106	639	445
108	108	hydrogen atom	"	"	"	3	2	free base	37	oily	531	265
109	109	6-n-butoxy	"	"	"	2	2	"	33	"	589	395
110	110	6-n-pentoxy	"	"	"	2	2	"	29	"	603	409
111	111	6-isopentoxy	"	"	"	2	2	"	26	"	603	409
112	112	hydrogen atom	4-methoxy	"	"	2	2	"	31	"	487	293
113	113	"	2-chloro	"	"	2	2	"	17	"	-	297
114	114	6-methyl	2,5-dimethoxy	"	"	2	2	"	21	"	531	337
115	115	hydrogen atom	3,4-dimethoxy	"	"	2	2	"	43	"	517	323
116	116	6-iodo	2,5-dimethoxy	"	"	2	2	"	56	"	643	443
117	117	6-isopropoxy	2-methoxy	"	"	2	2	"	37	"	545	351
118	118	"	4-methoxy	"	"	2	2	"	37	"	545	351
119	119	"	2-chloro	"	"	2	2	"	40	"	549	355

Table 3 (Contd.)

No.	No.	X	Y	R^1	Z	n	ℓ	Discrimination between free base and salt	Yield (%)	Melting point (°C)	Mass spectrum (m/e) M^+	Mass spectrum (m/e) Base peak ion
120	120	6-isopropoxy	3,4-dimethoxy	methyl	3,4-dimethoxy	2	2	free base	51	oily	575	381
121	121	6-ethoxy	2,5-dimethoxy	"	"	2	2	"	22	"	561	367
122	122	6-methoxy	"	"	"	2	2	"	51	"	547	353
123	123	hydrogen atom	"	"	3-methoxy	2	2	"	14	"	487	323
124	124	6-isopropoxy	"	"	"	2	2	"	13	"	545	381
125	125	hydrogen atom	"	"	4-methyl	2	2	"	22	"	471	323
126	126	6-isopropoxy	"	"	"	2	2	"	18	"	529	381
127	127	"	"	"	4-methoxy	2	2	"	28	"	545	381
128	128	hydrogen atom	"	"	4-chloro	2	2	"	20	"	491	323
129	129	6-isopropoxy	"	"	"	2	2	"	9	"	549	381
130	130	hydrogen atom	"	"	2,5-dimethoxy	2	2	"	26	"	517	323
131	131	6-isopropoxy	"	"	"	2	2	"	17	"	575	381
132	132	hydrogen atom	"	"	4-methoxy	2	2	"	48	"	487	323

Synthesis example 4

2-(2,5-Dimethoxyphenylacetylamino)-5-methyl-N-(2-dimethylaminoethyl)benzamide

0.50 g (1.5 mmol) of 2-(2,5-dimethoxyphenylacetylamino)-5-methylbenzoic acid (m.p. 163 to 164.5 °C) synthesized in the same manner as in Synthesis example 1 for 2-(2,5-dimethoxyphenylacethylamino)-5-isopropoxybenzoic acid was suspended in dichloromethane (10 ml), and then to the resulting mixture was added dropwise a dichloromethane solution containing 0.33 (1.6 mmol) of dicyclohexylcarbodiimide (DCC) under ice cooling. Subsequently, 0.14 g (16 mmol) of 2-dimethylaminoethylamine was added dropwise thereto and the mixture thus obtained was stirred for 2 hours at room temperature. The precipitates were filtered off and the mother liquid was concentrated by distillation. The thus obtained residue was purified by silica gel column chromatography (eluent; dichloromethane : ethanol=97 : 3) to obtain 0.41 g (yield 68 %) of 2-(2,5-dimethoxyphenylacetyamino)-5-methyl-N-(2-dimethylaminoethyl)benzamide.

m.p. 105 - 110°C

Example 133

2-(2,5-Dimethoxyphenylmethyl)-3-(2-dimethylaminoethyl)-6-methyl-4(3H)-quinazolinone hydrochloride (Compound No.24; Synthesis process C)

0.37 g (1 mmol) of 2-(2,5-dimethoxyphenylacetylamino)-N-(2-dimethylaminoethyl)benzamide and 200 mg of para-toluenesulfonic acid were heated in xylene (20 ml) under reflux for 3 hours . The reation mixture thus obtained was purified by silica gel column chromatography (eluent; 2 % ethanol/chloroform) to obtain 70 mg (20 %)

of 2-(2,5-dimethoxyphenylmethyl)-3-(2-dimethylaminoethyl)-6-methyl-4(3H)-quinazolinone as an oily substance. Subsequently, the thus obtained oily substance was dissolved in 1 ml of ethanol, and to the resulting soluion was added a 7 % hydrogen chloride-ethanol solution (2 ml). Further, ether was added to the reaction mixture thus obtained and the precipitated colorless crystals were collected by filtration to obtain 70 mg of the hydrochloride which is the desired compound. The melting point and infrared absorption spectrum of the above hydrochloride was identical with those of Compound 24 synthesized in Example 24, respectively.

Synthesis example 5

2-(2-Methoxyphenylmethyl)-3-(2-chloroethyl)-4(3H)-quinazolinone

A suspension of 3.0 g (10 mmol) of methyl ester of N-(2-methoxyphenylacetyl)anthranilic acid and 1.2g (20 mmol) of monoethanolamine in xylene was heated at 180. ^{o}C for 16 hours in a sealed tube. After cooling, the precipitated crystals were collected by filtration to obtain 0.7g (22 %) of 2-(2-methoxyphenylmethyl)-3-(2-hydroxyethyl)- 4(3H)-quinazolinone (m.p.: 154 - 155 ^{o}C). Subsequently, to 0.7 g (2.2 mmol) of this 3-(2-hydroxyethyl) derivative was added thionyl chloride (5ml) and the resulting reaction mixture was stirred at room temperature for 1 hour. An excess of the thionyl chloride was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent: dichloromethane) to obtain 0.14 g (20%) of 2-(2-methoxyphenylmethyl)-3-(2-chloroethyl)-4(3H)-quinazolinone. (m.p.: 109 - 111 ^{o}C).

Example 134

2-(2-Methoxyphenylmethyl)-3-(2-ethylaminoethyl)-4(3H)-quinazolinone (Compound No. 133; Synthesis process D)

A mixture of 328 mg (1 mmol) of 2-(2-methoxyphenylmethyl)-3-(2-chloroethyl)-4(3H)-quinazolinone and a 70 % aqueous ethylamine solution (0.6 ml) in ethanol (10 ml) was heated at 80 °C for 8 hours in a sealed tube. The solvent was distilled off under reduced pressure and to the residue thus obtained there was added a 10 % aqueous potassium carbonate solution, followed by extraction with dichloromethane. The thus obtained dichloromethane solution was dried over magnesium sulfate and then concentrated. The resulting residue was purified by silica gel column chromatography (eluent: 1 % ethanol-chloroform) to obtain 55 mg (16%) of 2-(2-methoxyphenylmethyl)-3-(2-ethylaminoethyl)-4(3H)-quinazolinone as an oily substance. Subsequently, the thus obtained quinazolinone was dissolved in ether (3 ml) and to the resulting solution was added a 10% HCl/ethanol solution. The precipitated crystals were collected by filtration to obtain the hydrochride of the captioned compound.

m.p.: 170 - 175 °C

Mass spectrum (m/e): 337 (M^+),
267 (Base peak ion)

Examples 135 to 136

2-(2-Methoxyphenylmethyl)-3-(substitued aminoalkyl)-4(3H)-quinazolinone derivatives (Compound Nos. 134 and 135)

The captioned compounds were synthesized in the same manner as in Example 134 except that the 70 % aqueous ethylamine solution was replaced by the corresponsing amines, respectively. The results obtained are shown in Table 4.

Table 4

Example No.	Compound No.	X	Y	$N(R^1)(R^2)$	n	Discrimination between free base and salt	Yield (%)	Melting point (°C)	Mass spectrum (m/e) M^+	Mass spectrum (m/e) Base peak ion
135	134	hydrogen atom	2-methoxy	cyclopentylamino	2	free base	41	oily	377	267
136	135	"	"	hexamethyleneimino	2	hydrochloride	50	135-145	-	112

Synthesis example 6

2-(2,5-dimethoxyphenylmethyl)-6-methyl-4(3H)-quinazolinone

A mixture of 3.15 g (9.6 mmol) of 2-(2,5-dimethoxyphenylacetylamino)- 5-methylbenzoic acid (m.p. 163 to 164.5 °C) obtainble by the same method as in Synthesis example 2 and 0.90 g (20ml) of formamide were heated at 160 °C for 3 hours. After cooling, the solidified residue was added to a mixed solution of ethanol (100 ml) and acetone (100 ml) and dissolved therein by heating. After cooling, the precipitated crystals were collected by filtration to obtain 1.45 g (yield 49 %) of 2-(2,5-dimethoxyphenylmethyl)-6-methyl-4(3H)-quinazolinone.

m.p.: 188 - 189 °C

Mass spectrum (m/e): 310 (M^+),
279 (Base peak ion)

Example 138

2-(2,5-Dimethoxyphenylmethyl)-3-(2-dimethylaminoethyl)-6-methyl-4(3H)-quinazolinone hydrochloride (Compound No. 24; Synthesis process E)

A suspension of 0.62 g (2 mmol) of 2-(2,5-dimethoxyphenylmethyl)-6-methyl-4(3H)-quinazolinone and 0.19 g (2 mmol) of 50 % sodium hydride in dioxane (10 ml) were stirred at room temperature for 1 hour. Then, to the resulting reaction mixture was added 0.22 g (2 mmol) of dimethylaminoethyl chloride dissolved in dioxane (10 ml), followed by heating at 60 °C for 5 hours. After cooling, to the mixture obtained were added 30 ml of water. The resulting mixture was extract d with dichloromethane and

the dichloromethane layer was concentrated under reduced pressure. The thus obtained residue was purified by silica gel column chromatography (eluent; dichloromethane: ethanol = 97 : 3) to obtain 0.10 g (yield 13 %) of 2-(2,5-dimethoxyphenylmethyl)-3-(2-dimethylaminoethyl)-6-methyl-4(3H)-quinazolinone as an oily substance. The thus obtained quinazolinone was dissolved in ether and to the resulting solution was added a 5 % hydrogen chloride-ethanol solution and the precipitated crystals were collected by filtration to obtain 2-(2,5-dimethoxyphenylmethyl)-3-(2-dimethylaminoethyl)-6-methyl-4(3H)-quinazolinone hydrochloride. The melting point and infrared absorption spectrum of this hydrochloride were identical with those of Compound 24 obtained in Example 24, respectively.

Example 139

2-(2,5-Dimethoxyphenylmethyl)-3-{2-(1-pyrrolidino)ethyl}-6-benzyloxy-4(3H)-quinazolinone (Compound No. 136)

2-(2,5-dimethoxyphenylmethyl)-3-{2-(1-pyrrolidino)ethyl}-6-hydroxy-4(3H)-quinazolinone (Compound No. 38) (90 mg, 0.2 mmol) and sodium hydroxide (16 mg, 0.4 mmol) were added to a mixed solvent of ethanol (10 ml) and water (5 ml). To the resulting reaction mixture were added benzyl chloride (40 mg, 0.3 mmol), followed by reflux for 1 hour, and then, to the mixture thus obtained further were added benzyl chloride (27 mg, 0.2 mmol), followed by reflux for further 1.5 hours. After concentration under reduced pressure, water was added thereto and the mixture obtained was extracted with dichloromethane. The dichloromethane solution was dried over magnesium sulfate and purified by silica gel column chromatography {eluent; ethanol (0 - 5%)-dichloromethane} to obtain 16 mg (15%) of 2-(2,5-dimethoxyphenylmethyl)-3-{2-(1-pyrrolidino)ethyl}-6-benzyloxy-4(3H)-quinazolinone.

Mass spectrum (m/e): 499 (M^+),
84 (Base peak ion)

Infrared absorption spectrum (IR) (cm^{-1}):
1655, 1585

Example 140

3-(2-Dimethylaminoethyl)-2-{2-(4-methoxyphenyl)ethyl}-4(3H)-quinazolinone (Compound No. 137; Synthesis process B)

A mixture of 295 mg (1 mmol) of 2-{2-(4-methoxyphenyl)ethyl}-4H-3,1-benzoxazin-4-one synthesized in the same manner as in Synthesis example 2 and 88 mg (1 mmol) of 2-dimethylaminoethylamine in xylene (5 ml) was heated under reflux for 2 hours. After the xylene was distilled off under reduced pressure, the crude crystals obtained were purified by silica gel column chromatography (eluent; 3 % methanol/methylene chloride) to obtain 260 mg (76 %) of 3-(2-dimethylaminoethyl)-2-{2-(4-methoxyphenyl)ethyl}- 4(3H)-quinazolinone.

m.p.: 73.5 - 74.5 °C

Mass spectrum (m/e): 351 (M^+),
58 (Base peak ion)

Infrared absorption spectrum (IR) (cm^{-1}):
1665 (C=O), 1600 (phenyl group)

Example 141

3-(2-Dimethylaminoethyl)-6-isopropoxy-7-methoxy-2-{3-(4-methoxyphenyl)propyl}-4(3H)-qunazolinone (Compound No. 138, Synthesis process B)

A mixture of 384 mg (1 mmol) of 6-isopropoxy-7-methoxy-2-{3-(4-methoxyphenyl)propyl}4H-3,1-benzoxazin-4-one synthesized in the same manner as in Synthesis example 2 and 88 mg (1 mmol) of 2-dimethylaminoethylamine in xylene (5 ml) was heated under reflux for 2 hours. After the xylene was distilled off, the crude crystals obtained were purified by silica gel column chromatographty (eluent; 3 % methanol/methylene chloride) to obtain 362 mg (80 %) of 3-(2-dimethylaminoethyl)-6-isopropoxy-7-methoxy-2-{3-(4-methoxyphenyl)propyl}-4(3H)-quinazolinone.

m.p.: 65.5 - 66.5 ^{o}C

Mass spectrum (m/e): 453 (M^{+}),
58 (Base peak ion)

m.p.: 65.5 - 66.5 ^{o}C

Mass spectrum (m/e): 453 (M^{+}),
58 (Base peak ion)

Infrared absorption spectrum (IR) (cm^{-1}):
1660 (C=O), 1605 (phenyl group)

Example 142

2-(2,5-Dimethoxyphenylmethyl)-3-(2-dimethylaminoethyl)-4(3H)-quinazolinone hydrochloride (Compound No. 16; Synthesis process A)

A mixture of 0.62 g (2 mmol) of N-(2,5-dimethoxyphenylacetyl) anthranilic acid and 0.36 g (3 mmol) of 2-dimethylaminoethylamine in xylene (5 ml) were heated under reflux for 24 hours. After cooling, the resulting reaction mixture was purified by silica gel column chromatography (eluent; chloroform: ethanol = 98 : 2) to obtain 0.10 g (yield 14 %) of 2-(2,5-dimethoxyphenylmethyl)-3-(2-dimethylaminoethyl)-4(3H) quinazolinone as an oily substance. 0.10 g of the oily substance thus obtained was dissolved in ethanol (1 ml) and then a 7 % HCl-ethanol solution (0.2 mol) was added thereto and the resulting reaction mixture was cooled overnight. The resulting colorless precipitates were collected by filtration to obtain 0.1 g of the hydrochloride which is the desired compound. This hydrochloride coincides with the compound obtained in Example 16 in melting point and infrared absorption spectrum.

Application example 1

Calcium antagonistic activity

Calcium antagonistic activity of the present compound was investigated by observing the effects on the calcium induced contraction of the isolated thoracic aorta in rats.

A piece of thoracic aorta was isolated from male Wistar strain rats weighing 350 - 450 g in order to prepare a

spiral specimen. This specimen was suspended in a Krebs-Henseleit solution free from calcium. The contraction was evoked by an application of $CaCl_2$ in the presence of 80 mM potassium so as to adjust the solution at a concentration of 10 mM Ca^{++}. The present compound to be tested was applied to the specimen which had been maximally contracted and was evaluated for its relaxing activity. The results obtained are shown in Table 5.

Table 5

Calcium antagonistic activity

Compound No.	Minimum effective concentration (μM)
1	1
13	3
14	1
15	0.3
19	0.3
20	0.3
26	1
30	0.3
31	1
47	0.1
50	0.3
63	0.3
64	0.3
89	0.3
93	0.03
102	0.03
103	0.1
114	0.1
116	0.03
121	0.03
diltiazem (Control)	0.3

Application example 2

Increasing activity of coronary blood flow

Male and female mongrel dogs weighing 8 to 17.5 kg were anesthetized with intravenous administration of sodium pentobarbital at a dosage of 30 mg/kg. Under artificial respiration the chest was opened on the left side at the level of the fourth intercostal space and the heart was exposed. The circumflex branch of left coronary artery just below the junction of the anterior descending branch of left coronary artery was isolated in a width of approximately 1 cm, and a flow probe was placed around this artery in order to measure the blood flow of the circumflex branch of left coronary artery by means of an electromagnetic flow meter. During the tests, systemic blood pressure was monitored, and data obtained from tests where the mean blood presure was less than 65 mmHg were excluded from the final data. The pharmaceutical compound to be tested was dissolved in physiological saline or 50 % ethanol/50 % physiological saline and the thus obtained solution was intravenously administered at a dosage of 1 ml/10 kg through a polyethylene catheter which had been provided within the left femoral vein. The increasing activity of the blood flow of the circumflex branch of left coronary artery was evaluated and expressed in terms of increase rate of the blood flow after the administration of the compound to that of before the administration of the compound. The results obtained are shown in Table 6.

Table 6

Inerease in coronary blood flow
(dog, 0.1 mg/kg iv)

Compound No.	Increase rate of coronary blood flow (%)
13	32.7
14	42.7
15	45.3
31	42.5
47	95.4
63	77.3
64	47.6
102	53.6
diltiazem (Control)	91.2

Application example 3

Antihypertensive activity

The compounds to be tested were administered orally to evaluate antihypertensive activity in spontaneously hypertensive rats (hereinafter SHR).

The average blood pressure of male SHR, 20 to 30 weeks old, was measured in a non-anesthetised and non restraint state, through a catheter which had been chronically implanted into the abdominal aorta through the right femoral artery, using an electromanometer. At the same time, the heart rate was measured by a tachometer triggered by the pulse pressure. The compound to be tested was suspended in a 1 % tragacanth solution. After

the concentration of the suspensions was adjusted in a volume of 5 ml/kg, the compound was administered orally to the SHR. The blood pressure and heart rate were measured 0.5, 1, 3, 6 and 24 hours after the administration. The results are shown in Table 7.

Table 7

Antihypertensive activity

Comp. No.	Oral dosage (mg/kg)	Average blood pressure before administration	Increase rate of average blood pressure after administration (%)	
			after 1 hour	after 3 hours
47	10	188	-12	-3
50	10	190	-17	-7
82	10	190	-24	-15
102	10	187	-11	-2
diltiazem	30	185	-8	0
(Control)	100	186	-28	-14

Application example 4

Acute toxicity test

Tests were made using groups each comprising five male ICR strain mice weighing 30 to 35 g and being kept under a fast for 18 hours. The compound to be tested was suspended in a 1 % tragacanth solution. After the concentration of the suspensions was adjusted in a volume of 40 ml/kg, the compound was administered orally to the mouse. The results are shown in Table 8.

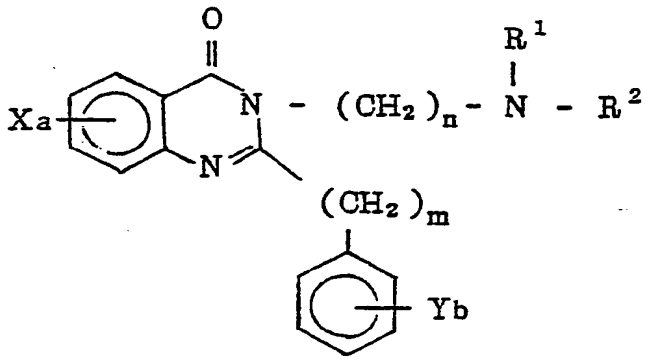
Table 8

Acute toxicity test (mouse, oral administration)

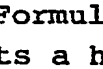
Comp. No.	LD50 (mg/kg)
13	700
31	1,000
47	750
50	700
63	1,200
82	750
102	1,000
diltiazem (Control)	650

Claims:

1. 2-Phenylalkyl-3-aminoalkyl-4(3H)-quinazolinone compound of Formula (1):



...(1)

wherein, X represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a phenoxy group, a benzyloxy group, a halogen atom or a hydroxy group; Y represents an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a benzyloxy group, a halogen atom or a nitro group; R^1 represents a hydrogen atom or an alkyl group having 1 to 5 carbon atoms; R^2 represents an alkyl group having 1 to 5 carbon atoms or a group of Formula (2) $-(CH_2)_\ell$-  [wherein, Z represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms or a halogen atom; c is an integer of 1 to 3; and ℓ is an integer of 1 to 5]; or R^1 and R^2 represent, together with the nitrogen atom to which they are attached, a cyclic amino group of the formula: $-N\overset{\frown}{\underset{\smile}{}}A$ [wherein, A represents an alkylene group having 2 to 6 carbon atoms or a group of the formula $-(CH_2)_2-O-(CH_2)_2-$]; a and b are independently an integer of 1 to 3; and n and m are independently an integer of 1 to 5,

or a pharmaceutically acceptable acid addition salt thereof.

2. The compound of Formula (1) according to Claim 1, in which

X represents

a hydrogen atom, a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, a sec-butyl group, a pentyl group, a methoxy group, an ethoxy group, an n-propoxy group, an isopropoxy group, an n-butoxy group, an sec-butoxy group, an n-pentoxy group, a phenoxy group, a benzyloxy group, a fluorine atom, a chlorine atom, a bromine atom, an iodine atom or a hydroxy group;

Y represents

a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, a sec-butyl group, a pentyl group, a methoxy group, an ethoxy group, an n-propoxy group, an isopropoxy group, an n-butoxy group, a sec-butoxy group, an n-pentoxy group, a benzyloxy group, a fluorine atom, a chlorine atom, a bromine atom, an iodine atom or a nitro group;

R^1 represents

a hydrogen atom, a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, a sec-butyl group, or a pentyl group;

R^2 represents

a methyl group, en ethyl group, an n-propyl, an isopropyl group, an n-butyl group, a sec-butyl group, a pentyl group, or a group of

Formula (2) $-(CH_2)_\ell$  (wherein, Z represents a hydrogen atom, a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, a sec-butyl group, a pentyl group, a methoxy group, an ethoxy group, an n-propoxy group, an isopropoxy group, an n-butoxy group, a sec-butoxy group, an n-pentoxy group, a fluorine atom, a chlorine atom, a bromine atom or an iodine atom); or

R^1 and R^2 represent, together with the nitrogen atom to which they are attached

an azilidino group, a pyrrolidino group, a pyperidino group, a hexamethyleneimino group or a morpholino group,

3. The compound of Formula (1) according to Claim 2 in which

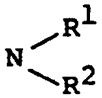
X represents

a hydrogen atom, a methyl group, an ethyl group, a chlorine atom, an iodine atom, a hydroxy group, a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, an n-butoxy group, an isobutoxy group, a sec-butoxy, an n-pentoxy group, an isopentoxy group, a phenoxy group, a chlorophenyl group or a methoxyphenoxy group when a is 1, or a dimethoxy group, a methoxy group and

an ethoxy group or a methoxy group and an isopropyl group when a is 2.

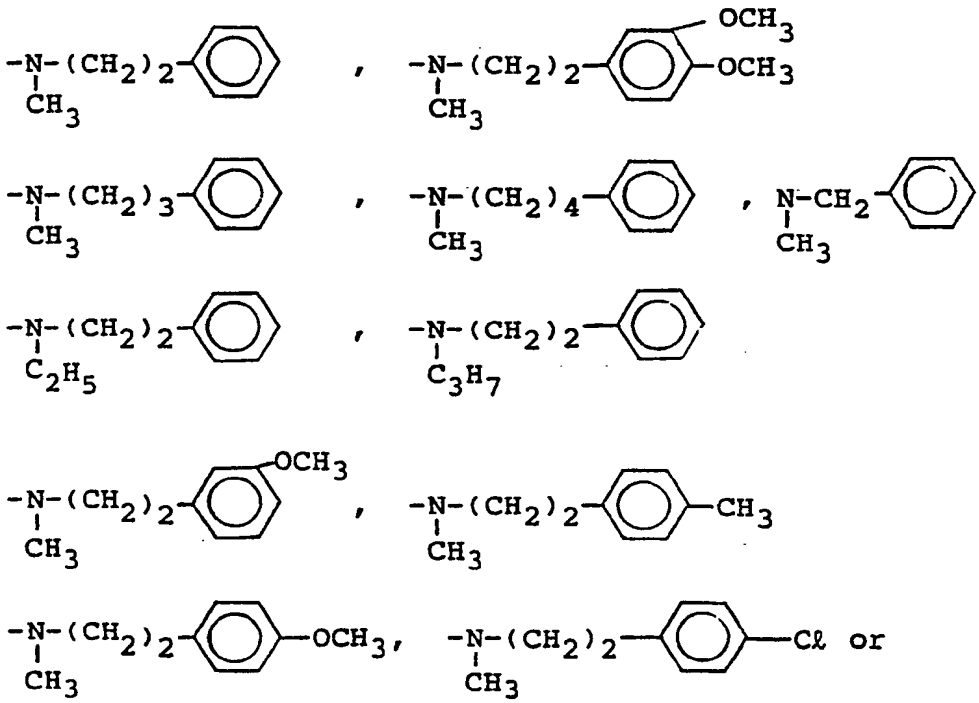
Y represents

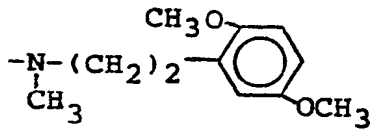
a chlorine atom, a bromine atom, a methoxy group, an ethoxy group, a methyl group, a nitro group, a benzyloxy group, or an isopropoxy group when b is 1, or a dimethoxy group when b is 2.



represents

a dimethylamino group, a pyrrolidino group, a diethylamino group, a morpholino group, a methylamino group, a cyclopentylamino group, a hexamethyleneimino group,

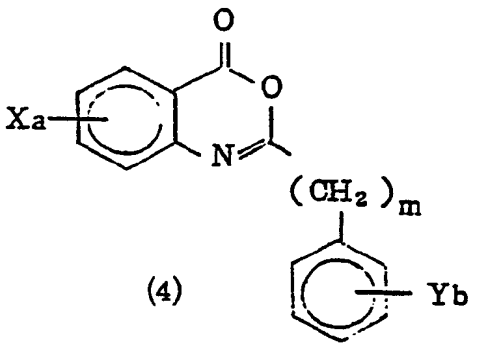




4. The compound of Formula (1) according to Claim 3, wherein the compound of Formula (1) is one selected from the group consisting of
2-(2,5-Dimethoxyphenylmethyl)-3-(3-dimethylaminopropyl)-6-isopropoxy-4(3H)-quinazolinone (Compound No.30),
2-(2,5-Dimethoxyphenylmethyl)-3-(2-pyrrolidinylethyl)-6-methyl-4(3H)-quinazolinone (Compound No.31),
2-(2,5-Dimethoxyphenylmethyl)-3-(2-dimethylaminoethyl)-6-isopropoxy-4(3H)-quinazolinone (Compound No.47),
2-(4-Methoxyphenylmethyl)-3-(2-dimethylaminoethyl)-6-isopropoxy-4(3H)-quinazolinone (Compound No.50),
2-(2,5-Dimethoxyphenylmethyl)-3-2-dimethylaminoethyl)-6-isopropoxy-7-methoxy-4(3H)-quinazolinone (Compound No.81),
2-(4-Methoxyphenylmethyl)-3-(2-dimethylaminoethyl)-6-isopropoxy-7-methoxy-4(3H)-quinazolinone (Compound No.82),
2-(2,5-Dimethoxyphenylmethyl)-3-[2-{N-(3,4-dimethoxyphenylethyl)-N-methylamino}-ethyl]-4(3H)-quinazolinone (Compound No.93),
2-(4-Methoxyphenylmethyl)-3-[2-{N-(3,4-dimethoxyphenylethyl)-N-methylamino}-ethyl]-4(3H)-quinazolinone (Compound No.112),
2-(4-Methoxyphenylmethyl)-3-[2-{N-(3,4-dimethoxyphenylethyl)-N-methylamino}-ethyl]-6-isopropoxy-4(3H)-quinazolinone (Compound No.118) and
2-(2,5-Dimethoxyphenylmethyl)-3-[2-{N-(3,4-dimethoxyphenylethyl)-N-methylamino}-ethyl]-6-isopropoxy-4(3H)-quinazolinone (Compound No.120).

5. A process for preparing the compound of Formula (1) in Claim 1 which comprises

reacting a compound of Formula (4)



(4)

wherein X, Y, a, b and m have the same meanings as defined in Claim 1,

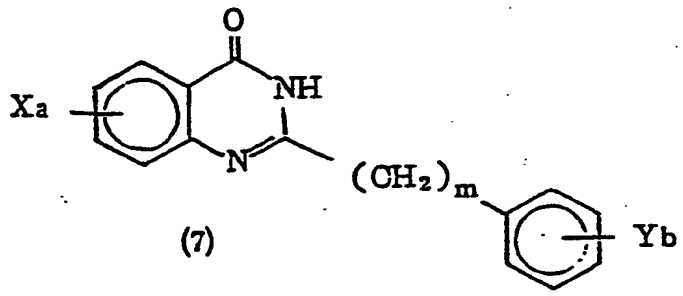
with a diamine of Formula (8)

$$H_2N-(CH_2)_n-\overset{R^1}{\underset{|}{N}}-R^2 \quad (8)$$

wherein R^1, R^2 and n have the same meanings as defined in Claim 1.

6. A process for preparing the compound of Formula (1) in Claim 1 which comprises

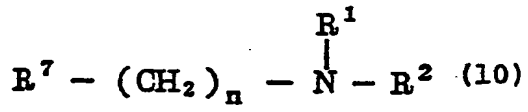
reacting a compound of Formula (7)



(7)

wherein X, Y, a, b and m have the same meanings as defined in Claim 1,

with an amine represented by Formula (10)



(10)

wherein R^1, R^2 and n have the same meanings as defined in Claim 1, and R^7 represents a halogen atom or a mesyloxy group or a tosyloxy group.

7. A pharmaceutical composition which comprises the compound of Formula (1) in Claim 1 or a pharmaceutically acceptable acid addition salt thereof as an active ingredient, and a pharmaceutically acceptable carrier.

8. The composition according to Claim 7, wherein the compound of Formula (1) in Claim 1 is one in Claim 2.

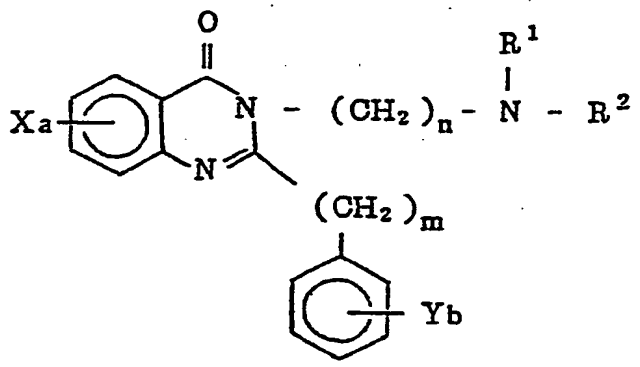
9. The composition according to Claim 8, wherein the compound of Formula (1) in Claim 2 is one in Claim 3.

10. The composition according to Claim 9, wherein the compound of Formula (1) in Claim 3 is one in Claim 4.

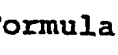
11. The use of the compound of Formula (1) in Claim 1 or its pharmaceutically acceptable acid addition salt for the preparing of a pharmaceutical composition for dilating blood vessels or reducing the level of blood pressure based on calcium antagonistic activity.

Claims for Austria

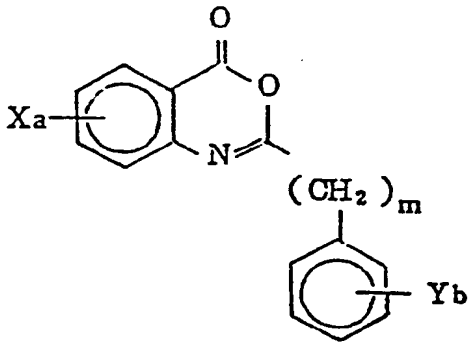
1. A process for preparing 2-Phenylalkyl-3-amino-alkyl-4(3H)-quinazolinone compounds for Formula (1):



...(1)

wherein, X represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a phenoxy group, a benzyloxy group, a halogen atom or a hydroxy group; Y represents an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a benzyloxy group, a halogen atom or a nitro group; R^1 represents a hydrogen atom or an alkyl group having 1 to 5 carbon atoms; R^2 represents an alkyl group having 1 to 5 carbon atoms or a group of Formula (2) $-(CH_2)_\ell$-  [wherein, Z represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms or a halogen atom; c is an integer of 1 to 3; and ℓ is an integer of 1 to 5]; or R^1 and R^2 represent, together with the nitrogen atom to which they are attached, a cyclic amino group of the formula: $-N\frown A$ [wherein, A represents an alkylene group having 2 to 6 carbon atoms or a group of the formula $-(CH_2)_2-O-(CH_2)_2-$]; a and b are independently an integer of 1 to 3; and n and m are independently an integer of 1 to 5,

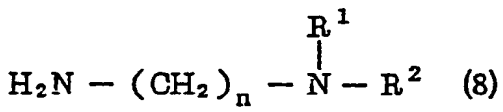
characterized by reacting a compound of Formula (4)



(4)

wherein X, Y, a, b and m have the meanings as defined hereinabove,

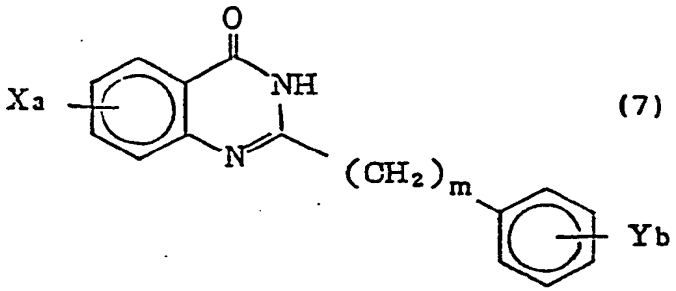
with a diamine of Formula (8)



(8)

wherein R^1, R^2 and n have the meanings as defined hereinabove.

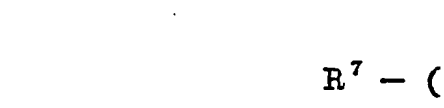
2. A process for preparing the compound of Formula (1) in Claim 1 which comprises reacting a compound of Formula (7)



(7)

wherein X, Y, a, b and m have the same meanings as defined in Claim 1,

with an amine represented by Formula (10)



$$R^7 - (CH_2)_n - \overset{R^1}{\underset{|}{N}} - R^2 \quad (10)$$

wherein R^1, R^2 and n have the same meanings as defined in Claim 1, and R^7 represents a halogen atom or a mesyloxy group or a tosyloxy group.

3. The use of the compound of Formula (1) in Claim 1 or its pharmaceutically acceptable acid addition salt for the preparing of a pharmaceutical composition for dilating blood vessels or reducing the level of blood pressure based on calcium antagonistic activity.